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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,294	02/17/2004	Steven W. Dow	021819-000200US	8023

20350 7590 03/19/2008

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
03/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,294	DOW ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/14/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of December 14, 2007, to the non-final action dated June 15, 2007 has been entered. Claims 1-22 are pending in the application. Claims 12 and 15 have been amended. No claims were cancelled or newly added. Claims 1-22 are currently under examination.

Response to Claim Rejections - 35 USC § 112- Second Paragraph

Claim 12 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite, in the previous office action dated June 15, 2007.

In view of Applicants' amendment of the claim to recite language that is not in conflict with the limitation of base claim 1 with regard to oligonucleotide size range, thus obviating the ground for rejection, the previous rejection is hereby withdrawn.

Response to Claim Rejections - 35 USC § 112 – Written Description

Claims 1-22 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The rejection set forth on pp. 2-4 of the previous office action dated June 15, 2007 is maintained for reasons of record.

The previous office action noted that the instant claims embrace an enormous number of oligonucleotides lacking CpG motifs, constituting a genus, and that the specification fails to disclose a representative number of the numerous ribonucleotides, deoxyribonucleotides or chemically modified oligonucleotides of any size or sequence composition, lacking CpG motifs, that would further be able to elicit a therapeutic systemic, non-antigen-specific immune response. The instant specification does not describe the structure or functional nature of the numerous oligonucleotides, other than a single distinct sequence for each of a 25mer, 50mer, 75mer and a 100mer, with no IFN-γ release demonstrated for the 100mer. The specification is further silent on the specific characteristics, or sequence motifs of any non-CpG oligonucleotides, that may

contribute to a therapeutic immune response, in view of the findings of the prior art. The claims thus embrace a claimed genus that encompasses immune response eliciting non-CpG oligonucleotide sequences yet to be discovered.

Applicants traverse the rejection, arguing that the specification describes the claimed oligonucleotide(s) being greater than 10 to about 500 nucleotides in length and stating "Immune activation by nucleic acid:lipid complexes of the present invention can be induced by eukaryotic as well as prokaryotic nucleic acids, indicating that there is some property of the nucleic acid:lipid complexes that is inherently immune activating, regardless of the source of the nucleic acids." Thus, persons of ordinary skill in the art would recognize that the Applicants invented what is claimed because the specification clearly describes the claimed invention. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it is noted that the longest oligonucleotide sequence exemplified in the specification is a 100mer deoxynucleotide, having no demonstrated ability to elicit IFN-γ release in an *in vitro* assay. Further, the issue is not the disclosure of any non-CpG oligonucleotide sequence *per se*, but rather, whether non-CpG oligodeoxynucleotides, or oligoribonucleotides of any sequence or chemical modification, greater than 10 to about 500 nucleotides in length, and further capable of eliciting a therapeutic systemic non-antigen specific immune response in a mammal, were described in sufficient detail to demonstrate possession of the claimed genus by Applicants at the time of the instant invention.

The instant claims, embrace any oligonucleotide ranging in size from more than 10 to about 500 nucleotides in length that lacks a CpG motif. However, any such oligonucleotide is not necessarily capable of eliciting a systemic, non-antigen specific therapeutic response in a mammal, as said response is further dependent on specific sequences that so far remain undefined and are not apparent from the three oligonucleotides disclosed in the instant specification.

Applicants argue that they are not required to know the mechanism by which their invention works. Further stating: "There are many structural features of the claimed oligonucleotide:liposome composition that can account for the elicitation of the claimed immune response. For example, the claimed oligonucleotides have phosphate backbones, sugar moieties, nucleoside residues, and secondary or higher order structure. The higher order structure of the

oligonucleotides may be impacted by the presence of the liposome delivery vehicle, for another example. Any of the structures may participate in the elicitation of the claimed immune response."

In response, it is apparent from Applicants' admission that there is no established nexus between non-CpG oligonucleotide structure and the ability to elicit a systemic immune response. MPEP 2163, which states: [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated: It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Applicants are further directed to MPEP 2163 II: If the application as filed does not disclose the complete structure (or acts of a process) of the claimed invention as a whole, determine whether the specification discloses other relevant identifying characteristics sufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. For example, if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. In contrast, without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal

structure is highly unlikely. In this latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"); *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984)

Thus, the previous rejection is maintained for claims 1-22 for reasons of record, and the foregoing discussion.

Response to Claim Rejections - 35 USC § 112 - Lack of Enablement

Claims 1-22 stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The rejection set forth on pp. 4-8 of the previous office action dated June 15, 2007 is maintained for reasons of record.

Applicants traverse the rejection, arguing that they have specifically enabled a therapeutic composition of the invention, by quoting various paragraphs from the specification, and with specific reference to Examples 12-15, state that the Examples and Figures 30 and 31 demonstrate that a therapeutic composition comprising a liposome delivery vehicle and an isolated oligonucleotide of either a 25, 50, 75, or 100mer containing no CpG motifs significantly elicits a systemic, non-antigen specific immune response in a mammal as measured by an increase T-cell and B-cell activation. Applicants' arguments have been fully considered, but are not found persuasive

As previously indicated, the claims have been examined in view of the as filed specification, and embrace a method for using a composition comprising a liposome delivery vehicle and an oligonucleotide containing no CpG motifs composition in a treatment of tumors in a mammal when administered as a therapeutic vaccine. The specification states: "The above-mentioned method and compositions of the present invention have the advantages of eliciting a systemic, non-antigen specific immune response in a mammal, and more particularly, of eliciting a systemic, anti-viral immune response in a mammal. Additionally, the method and composition of the present invention can elicit a systemic, anti-tumor immune response in a mammal. Such

an anti-tumor immune response can result in the reduction of a tumor in the mammal." (paragraph [0015], p. 4).

Applicants' arguments regarding the combination of oligonucleotide and liposome delivery vehicle are not found persuasive, because the previous office action set forth detailed observations regarding the deficiencies in Examples 12-15 that included the delivery of the combination therapeutic composition. For instance, Example 12 describes the i.v. injection of oligonucleotides lacking CpG motifs, ranging in size from 10 to 100 nucleotides into mice. The results are presented in Figure 30 and showed that while some activation of $CD8^+/CD69^+$ cells was detectable for oligonucleotides of 25 and longer lengths, the response was inferior in all cases, compared to a control 20 mer containing two CpG motifs, and contrary to the statement in paragraph [00228] of the instant specification, the responses were not as great as that elicited by the CpG containing oligonucleotide. Further, not only is there no apparent correlation between oligonucleotide size and CD69 activation (as evidenced by a decrease in activation in the 75 mer and 100 mer oligos from that seen with a 50mer), no 20 mer was included in the group of oligonucleotides lacking CpG to correspond to the size of control oligonucleotide.

Example 14 describes the i.v. injection into mice of oligonucleotides lacking CpG motifs, wherein the oligonucleotides were either a 10mer or a mixture of 50mer and 75 mer, followed by the isolation and culture of spleen cells for measuring IFNγ release. Here, the results from the 100 mer oligonucleotide were omitted, and IFNγ release was only detectable for the mixture of 50mer and 75 mer. As the positive controls in the experiment included plasmid DNA, it is not clear what conclusions may be derived by such non-analogous comparisons. It is noted that the 20mer control oligonucleotide containing two CpG sequences, yielded very little measurable IFNγ release. Applicants have failed to address the deficiencies in the experiment.

Example 15 describes the results obtained from an experiment similar to that noted in Example 14, except that IFN-α release was measured. Again, only the mixture of 50mer and 75 mer oligonucleotides resulted in an increase in IFN-α production over that observed with the CpG oligonucleotide. However, as the oligonucleotides are of different lengths and sequences, no definitive conclusions can be drawn from the experiment. It is further noted that the results from Examples 14 and 15, depicted in Figures 32 and 33 are not directly relevant to the instant

claims, as the claims are not directed to a mixture two different oligonucleotides, but rather a single oligonucleotide. Applicants have also failed to respond to the deficiencies in Example 15. Moreover, none of the examples using oligonucleotides lacking CpG motifs, included the assessment or evaluation of tumors correlate the immune responses generated with any therapeutic effect on any disease or infection. The specification is further silent on the sequence specific effects of the oligos, or the minimum size of an oligonucleotide required to elicit a cytokine response, or whether the cytokine release measured for some of the CpG deficient oligonucleotides would constitute a therapeutically effective amount in the treatment of any disease or infection. The previous office action therefore highlighted the deficiencies in the Examples, and as such analysis is in accord with the *Wands* factors, that include the working examples and the amount of direction or guidance presented, the Examples fail to support an enablement for the claimed invention.

Applicants argue that even if the CpG oligo response were significantly better for producing B and T-cell proliferation than the non-CpG oligonucleotides, that does not mean that the specification is not enabled for the four oligos which are statistically significant from the negative control. Figures 32 and 33 clearly show that that non-CpG compositions as tested using a mixture of 50 and 75 mer oligonucleotides have a significant effect on IFNγ, and IFNα.

Such is not found persuasive, because Figures 32 and 33 only show an effect only with a mixture of 50 mer and 75 mer, (i.e. SEQ ID NOS: 4 and 5), and not four oligonucleotides. Further, as the oligonucleotides are of different lengths and sequences, no definitive conclusions can be drawn from the experiment. It is noted again that the results from Examples 14 and 15, depicted in Figures 32 and 33 are not directly relevant to the instant claims, as the claims are not directed to a mixture two different oligonucleotides. Moreover, none of the examples using oligonucleotides lacking CpG motifs, included the assessment or evaluation of tumors, or the therapeutic effect of the oligonucleotide compositions in a mammal. The specification is further silent on the sequence specific effects of the oligos, or the minimum size of an oligonucleotide required to elicit a cytokine response, or whether the cytokine release measured for some of the CpG deficient oligonucleotides would constitute a therapeutically effective amount in the treatment of a tumor.

The prior art of Auf et al. (Clin. Cancer Res. 7: 3540-3543; 2001), describes broad immunostimulatory activity by phosphorothioate oligodeoxyribonucleotides containing CpG motifs (CpG-ODNs), and induced rejection of glioma cell tumors in rats (Abstract). However, when the authors tested ODNs lacking CpG motifs, they observed, that the ODNs did not lead to significant tumor inhibition (Fig. 1, p. 3541).

The post-filing art of Vollmer et al. (Immunology 113:212-223; 2004), teaches that oligodeoxynucleotides lacking CpG dinucleotides are less potent than CpG ODN and the mechanism by which they stimulate leucocytes is not understood. Further, activation of B cells by non-CpG ODN was shown to require a new sequence motif. (Abstract). The authors further noted that the magnitude of stimulation of Toll like receptor 9 via non-CpG ODN was always inferior to that with CpG ODN, and the extent of NFκB stimulation was dependent upon the thymidine content of the non-CpG ODN (second column, p. 220). Additionally, noting: "Without a phosphorothioate backbone, the presence of CpG dinucleotides becomes more critical for immune stimulation. Only a few reports describe immune stimulation mediated by phosphodiester non-CpG ODN, and they had usually to be added at extremely high concentrations and on several occasions." (first column, p. 221). Also observing: "non-CpG ODN induce Th2-dominated immune responses in contrast to Th1-biased effects seen with CpG ODN…as non-CpG ODN appear to lack one of the most important features of CpG ODN, the efficient stimulation of Th1-like cytokines, including type I interferons." (first column, p. 221).

In view of the deficiencies of the instant specification, made of record, and the teachings of the prior art, a person of skill in the art would therefore have to engage in additional undue experimentation to develop a composition comprising any liposome and an oligonucleotide (that may further be a ribonucleotide) of any size or sequence composition that when administered to a mammal, would have a therapeutic effect.

Thus, the rejection of the claims is maintained for reasons of record, and the foregoing commentary.

Conclusion

Claims 1-22 are not allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, Art Unit 1633

/Anne Marie S. Wehbe/
Primary Examiner, Art Unit 1633